

ADVERSE REACTIONS OF NITROFURANTOIN, TRIMETHOPRIM AND SULFAMETHOXAZOLE IN CHILDREN

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ABSTRACT

Purpose: Many children with urological disease require long-term treatment with antibiotics. In many cases the choice of medical instead of surgical management hinges on the implied safety of certain drugs. Recently some groups have advocated subureteral injection procedures to avoid long-term antibiotics for low grade reflux. We present a concise and relevant review on the use and adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children.

Materials and Methods: We reviewed the literature regarding the safety and toxicity of these drugs. Information regarding absorption, excretion and dosing was also gathered to explain better the mechanisms of toxicity.

Results: Adverse reactions in children reported in the literature related to nitrofurantoin are gastrointestinal disturbance (4.4/100 person-years at risk), cutaneous reactions (2% to 3%), pulmonary toxicity (9 patients), hepatotoxicity (12 patients and 3 deaths), hematological toxicity (12 patients), neurotoxicity and an increased rate of sister chromatid exchanges. Adverse reactions in children related to trimethoprim/sulfamethoxazole are almost exclusively due to the sulfamethoxazole component, including cutaneous reactions (1.4 to 7.4 events per 100 person-years at risk), hematological toxicity (0% to 72% of patients) and hepatotoxicity (5 patients). The majority of adverse reactions were found in children on full dose therapy and not prophylaxis.

Conclusions: The use of nitrofurantoin, trimethoprim and sulfamethoxazole is safe in children for long-term prophylactic therapy. The antibiotic safety issue should not be misconstrued as an argument for surgical therapy, whether minimally invasive or not. Adverse reactions exist to these medicines but they are less common than seen in adults, presumably because of the lower dose used for therapy, and the lack of significant comorbidities and drug interactions in children. Serious side effects are extremely rare and most are reversible by discontinuing therapy. The extremely low potential for significant adverse reactions should be discussed with parents.

KEY WORDS: urologic diseases, sulfonamides, trimethoprim, nitrofurantoin, adverse effects

Urologists treating pediatric patients have experienced a shift in treatment paradigms in the last 2 to 3 decades. Many children with reflux, megaureter and/or ureteroceles require long-term treatment with medications. In many cases the choice of medical instead of surgical management hinges on the implied safety of certain drugs. Medicines such as nitrofurantoin (NFN), sulfamethoxazole (SMX) and trimethoprim (TMP) have alleviated or postponed the need for surgery in many children.¹

Many parents who are presented with the option of medical management are excited by the idea of avoiding surgery and yet concerned about the extended use of antibiotics. Recently some groups have advocated performing minimally invasive subureteral injection procedures to avoid long-term antibiotics for low grade reflux. The urologist dealing with these families is oftentimes questioned about adverse reactions to the medicines. Many of the known side effects have been reported in adults and do not necessarily pertain to the pediatric population. Other allergic reactions such as rashes might occur more frequently in children. Most clinical trials of efficacy or safety performed by drug manufacturers do not include pediatric patients. Therefore, we must rely on independent epidemiological studies and anecdotal reports for this information.²

There is little information directly related to the pediatric use of these medicines to help guide urologists. We have

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extrapolated and consolidated all pertinent published information dealing with adverse reactions in pediatric patients who have been treated with NFN, TMP or TMP/SMX, the most commonly prescribed long-term antibiotics for preventing urinary tract infection (UTI). We have attempted to provide the clinician with a useful reference for specifically addressing these issues.

MATERIALS AND METHODS

The available English language literature was reviewed to identify all cases of adverse reactions to NFN, TMP and TMP/SMX. We searched the PubMed and Cochrane databases for pertinent reports. All reports of adverse reactions were included in this review. We did not exclude reports involving multiple medications that might have contributed to adverse reactions. Most reports did not re-challenge the patient with the suspected drug to confirm causality. Indications for antibiotic use were not limited to UTI prophylaxis. Reports of several adverse reactions were for indications other than UTI prophylaxis.

NITROFURANTOIN

NFN is a broad-spectrum antibiotic of the nitrofurantoin family that was introduced into clinical practice in 1953. Its spectrum of *in vitro* susceptibility includes the majority of *Escherichia coli*, *Citrobacter* species, group B streptococci, enterococci, *Staphylococcus aureus*, *S. epidermidis*, *Klebsiella pneumoniae* and *Enterobacter* species. Resistance to

this drug has remained virtually unchanged since its discovery, which makes it an attractive antimicrobial for long-term prophylaxis. The drug is believed to inhibit acetylcoenzyme A, interfere with bacterial carbohydrate metabolism or disrupt the normal process of cell wall formation.

NFN is predominantly absorbed in the proximal small intestine. It has 87% bioavailability on an empty stomach and 94% bioavailability when taken with food. It is excreted entirely in the urine and bile with approximately 40% of the ingested drug excreted intact in the urine after a plasma half-life of only 20 minutes. NFN does not penetrate tissues well and, therefore, it should not be used to treat kidney or prostate infections.

NFN is available as an oral suspension (25 mg/ml), tablets (50 and 100 mg) and parenteral liquid (180 mg/20 ml). Treatment for active infection in children is 5 to 7 mg/kg daily divided into 4 doses. Prophylactic dosing is 1 to 2 mg/kg daily.³ NFN is excreted by the urine through glomerular filtration and tubular secretion. Dosing should be modified in patients with renal insufficiency. Only modest increases in serum concentration are seen in patients with uremia, presumably due to its biliary excretion.

NFN has been associated with a number of adverse reactions. Many reports have not been confirmed by tissue diagnosis and re-challenge, as would be appropriate to establish a causal relationship between drug and reaction. Of course, this is not practical or ethical in most situations. These reactions range from minor allergic reactions to major toxicities, including death. Most major toxicities make up only a small fraction based on the cumulative doses given. Most adverse reactions have been reported at least once in children, prompting some groups to recommend curtailing the use of this medicine in children.⁴ Despite extensive worldwide use of NFN in the last 50 years, there have been only 2 articles that specifically deal with adverse reactions in children.^{5,6}

Gastrointestinal. Abdominal discomfort, nausea and vomiting associated with the use of NFN are the most commonly reported adverse reactions in adults and children.^{5,7,8} Many gastrointestinal side effects are probably not reported to national registries because they are minor reactions. Reported data likely under represents the true incidence. Nausea and vomiting were reported to be 4.4/100 person-years at risk in children younger than 16 years in 1 study.⁵ There was 1 reported toxic gastrointestinal reaction (1.1%) in 95 pediatric patients younger than 15 years in a closely monitored hospital setting.⁸ Gastrointestinal side effects usually develop within week 1 of therapy and they are more likely to occur in women than in men or children.⁸ Newer formulations of NFN in a macrocrystalline form have decreased the incidence of these side effects in adults.⁹

Cutaneous/allergic. Cutaneous lesions are the second most common adverse reaction related to NFN therapy.^{5,7,10} Cutaneous and allergic reactions usually manifest as macular, maculopapular and urticarial lesions. Most cutaneous reactions occur within month 1 of treatment.⁷ In a prospective surveillance study in hospitalized patients including adults, only 15 of 757 uses (2%) resulted in a cutaneous reaction.⁸ A 3.2% rate of allergic reactions was found in children younger than 15 years. Cutaneous drug reactions due to NFN have not been reported to be fatal in children and they are reversible with discontinuation of therapy.

Pulmonary. Pulmonary complications associated with NFN use are the most well known among practitioners with an incidence of 0.0009% in all patients.¹¹ These adverse reactions result in interstitial pneumonitis and can be further subdivided into 3 categories, namely acute, subacute and chronic reactions based on the duration of treatment.¹² A report from the national monitoring center for adverse reactions in Sweden reported 447 cases of pulmonary reactions to NFN in a 10-year period and only 3 (0.7%) involved children

(ages 5, 13 and 15 years).¹³ All were classified as mild acute pulmonary reactions, which subsided after discontinuation of the medicine.

Corraggio et al reported on 6 pediatric patients in their evaluation of the United States Food and Drug Administration Spontaneous Reporting System for adverse drug reactions.⁶ One patient had an acute reaction with resolution after discontinuation and 3 of 5 with chronic interstitial pneumonitis also showed resolution. No followup data were available on the remaining 2 patients. These findings prompted the group to conclude that the use of NFN in the pediatric population was safe and calls to curtail its use were unwarranted. In a more recent epidemiological study using a national database from Finland a group evaluated 921 children on long-term NFN prophylaxis and found no adverse pulmonary reactions in the study population in a 10-year period.⁵

Hepatic. Hepatotoxicity represents the most lethal adverse reaction associated with NFN with 3 reported deaths in children.^{6,14} The range of histopathological changes has been characterized in adults as cholestasis, necrosis and chronic active hepatitis.¹⁵ The mechanism of injury has been suggested to be an immunological reaction.¹⁶ In adults hepatic adverse reactions are more common in females than in males (89% vs 11%).^{10,15} However, in the 12 reported pediatric cases an approximate equal male and female incidence was identified.

Hepatotoxicity occurred after a mean of approximately 4 months of therapy, suggesting a dose dependent phenomenon.^{6,14} In 1 case report a child had centrilobular cholestasis 1 week after drinking the milk of a cow treated with NFN.¹⁷ In general, assessing causality in cases of hepatic toxicity is difficult because of the need for liver biopsy and drug rechallenge.

Hematological. Hemolytic anemia is the most well-known hematological adverse reaction associated with NFN.¹⁸ This adverse reaction is commonly associated with patients who have glucose-6-phosphate dehydrogenase deficiency. Red blood cells in these patients are unable to handle oxidant stress. A review revealed an incidence of 1 case per 100,000 courses of therapy.¹⁹ There were no cases in neonates. However, a recent case report from France underscores the importance of avoiding NFN late in pregnancy and during month 1 of life with a report of hemolytic anemia in a neonate in the first hours of life.²⁰ NFN is contraindicated in the first few months of life because of the inability of the immature liver to handle oxidant stress.

Other blood dyscrasias have been reported in children, including neutropenia, methemoglobinemia and agranulocytosis.^{5,6} One fatality was reported in this group of patients.

Neurotoxicity. Peripheral neuropathy is the most common neurological adverse reaction. This has been described as a sensorimotor polyneuropathy, first as paresthesias and dysesthesias beginning in the distal extremities.²¹ The incidence of this reaction in all patients has been reported at 0.0007%.¹¹ Coraggio et al reported this condition in 15 children from a review of the literature, and Food and Drug Administration data.⁶ The majority of these patients had impaired renal function. There was 1 report of benign intracranial hypertension in a 10-month-old boy.²² All reported cases with followup data in children showed resolution after discontinuation of therapy.

Cancer. An increased risk of transitional cell carcinoma in adults with a history of NFN treatment was detected in 1 epidemiological case-control study.²³ A recent prospective study specifically looking at the rate of chromosomal aberrations and sister chromatid exchanges in children undergoing treatment for UTI (5 to 8 mg/kg daily for 7 days) and subsequent prophylaxis (1 to 2 mg/kg daily for 1 to 12 months) showed no difference in chromosomal aberrations in children before and after NFN therapy.²⁴ However, there was a sta-

tistically significant correlation between cumulative dose and sister chromatid exchange frequency in children after 1 month of therapy. This group concluded that further evaluation is needed to elucidate the genetic safety of NFN.

TRIMETHOPRIM/SULFAMETHOXAZIDE

TMP/SMX is a combination of 2 drugs that inhibit bacterial folate synthesis. It has been available in the United States since 1973. SMX inhibits the synthesis of dihydrofolic acid from para-aminobenzoic acid. TMP inhibits the subsequent conversion to tetrahydrofolic acid, the active form of folic acid. Folate is an essential nutrient for thymidine synthesis in humans and bacteria. Bacteria are reliant on folate synthesis, whereas mammals predominantly acquire folate in the diet. This allows for the specific inhibition of bacterial growth without compromising the host. The TMP component inhibits mammalian dihydrofolate reductase to a certain degree, although it inhibits the bacterial enzyme 50,000 times more avidly.

The spectrum of activity for TMP/SMX primarily includes gram-negative bacilli and certain *Staphylococcus* species. The majority of *E. coli*, *Klebsiella*, *Enterobacter*, *Providencia*, *Morganella*, *Citrobacter*, *Acinetobacter*, *Shigella*, *Salmonella*, *Hemophilus influenzae*, *Streptococcus* group A (*S. viridans*, *S. agalactiae* and *S. pneumoniae*), *S. epidermidis* and methicillin resistant *S. aureus* strains are susceptible.

The pharmacokinetics of TMP/SMX have been evaluated in children from ages 3 months to 10 years.²⁵ After a single dose ingestion of 20 mg TMP and 100 mg SMX/5 ml a mean serum concentration of 1.0 µg/ml TMP and 20 µg/ml SMX was achieved in 4 hours. The serum concentration of SMX does not seem to vary with age, although there was a trend for serum TMP concentration to increase with age. The half-life of TMP and SMX is 9 to 15 hours.²⁶

TMP/SMX is almost completely absorbed from the gastrointestinal tract, resulting in minimal fecal excretion.²⁶ Approximately 50% of a TMP dose is excreted unchanged in urine.²⁷ SMX undergoes significant conjugation and acetylation by the liver with only 20% of a dose eliminated unchanged in urine.²⁷ Renal insufficiency prolongs elimination and decreases urinary excretion. Dosing should be adjusted in patients with a creatinine clearance of less than 30 ml per minute.

The dose of TMP/SMX is based on the TMP component. The fixed combination drug is sold under different proprietary names and is available in oral tablet (80 mg single strength and 160 mg double strength) and oral suspension (40 mg/5 ml) as well as parenteral injection forms. Treatment for active infection in children is dosed at 8 to 10 mg/kg TMP daily divided into 2 daily doses. Prophylactic therapy is given at 2 mg/kg TMP daily, preferably at bedtime.³

Trimethoprim monotherapy. Although the TMP/SMX dose is based on the TMP component of the medicine, most adverse reactions related to its use are attributed to SMX. An epidemiological study in the United Kingdom evaluating mortality associated with drugs in a 35-year period showed antibiotics to be the third most common cause of death due to medications in children.²⁸ TMP/SMX was the leading cause of mortality with 6 reported cases (19%) in this period. Because of this, some groups have advocated TMP monotherapy.²⁹

In adults 3 double-blind studies showed that the combination drug TMP/SMX was not superior to TMP monotherapy for the treatment of UTI.³⁰⁻³² However, a fourth study showed the superiority of combination therapy over monotherapy for the treatment of chronic UTI. The majority of patients in this study had abnormalities of the urinary tract.³³

Smellie et al prospectively evaluated 334 children with recurrent UTI placed on prophylactic TMP/SMX or TMP

alone.³⁴ Approximately half of these patients had vesicoureteral reflux or renal scarring. The recurrence rates were 1/22 child-years in children receiving TMP/SMX and 1/18 child-years in those receiving TMP alone. All except 1 reinfections were resistant to TMP. The side effect profile was minimal and similar in the 2 groups.

Another prospective randomized study in children compared TMP monotherapy to NFN for the prevention of UTI.³⁵ Children were stratified into groups with abnormal urography, reflux and normal urography. In patients with urological abnormalities the number of infections yearly was 1.19 to 1.37 with TMP compared to 0.12 to 0.15 with NFN. This difference was less apparent in the normal urography group of children, namely 1.26 with TMP and 0.74 with NFN. Although side effects were more common with NFN, most were related to the bad taste of the medicine and stomach upset. Rash was the worst adverse reaction, which occurred in 3 patients on NFN and 2 on TMP.

The concern for increased resistance to TMP monotherapy along with suboptimal prophylactic coverage has been a concern of many clinicians, which is why monotherapy has not gained wide acceptance for the treatment or prophylaxis of UTI, especially in patients with structural abnormalities of the urinary tract. Recently the rate of TMP/SMX resistant *E. coli* strains has been increasing in certain regions of the country.³⁶ Adverse reactions to TMP are included in the appropriate categories described.

Cutaneous. Cutaneous reactions associated with TMP/SMX are the most common and well-known adverse reactions in children. The incidence in children younger than 2 years is 7.4 events per 100 years at risk.⁵ This number decreases significantly to 1.4 events per 100 years at risk in children 2 to 15 years old, presumably due to prior exposure and the exclusion of those at known risk for allergic reaction. The incidence for TMP monotherapy was reported at 0 and 2 events per 100 years at risk in children younger than 2 and 2 to 15 years old, respectively. The Boston collaborative group found rashes to be the most common side effect of TMP/SMX in children, accounting for 70% of all adverse reactions.³⁷ One study showed TMP/SMX to be the most common cause of cutaneous drug eruptions in all children on medications.³⁸

Cutaneous reactions are hypersensitivity reactions and they usually manifest immediately after exposure or re-exposure to the drug, unlike other adverse reactions, which might only manifest at high doses or after prolonged therapy. The spectrum of cutaneous reactions to TMP/SMX includes urticaria, maculopapular rash, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).³⁹ Urticaria and maculopapular rash are by far the most commonly observed skin reactions. Treatment is discontinuation of the medicine with complete resolution.

Fixed drug eruption is a sharply demarcated, round, erythematous to violaceous 2 to 10 cm plaques occurring after drug ingestion. The diagnostic hallmark is recurrence at previously affected sites. The 2 largest series of children with fixed drug eruption showed that TMP/SMX or SMX alone was the suspected cause in approximately 70%.^{40,41} Fixed drug eruptions are short in duration of onset (1 to 8 hours) and show complete resolution with discontinuation of the offending drug.

Erythema multiforme, SJS and TEN are a spectrum of rare acute bullous diseases characterized by skin lesions and mucosal surface involvement.⁴² The diseases are listed in increasing severity and they represent the most dangerous cutaneous reactions associated with TMP/SMX.⁴³ The distinction among these diseases is made by the identification of specific target lesions, quantification of the extent of skin and mucosal involvement, presence of bullae and pathological data.⁴² A consensus as to the differentiating factors among

these diseases was not established until 1993. Consequently many cases prior to 1993 might have been reported incorrectly.

The etiology of these disorders is not uniquely associated with drug ingestion. More commonly these conditions are associated with infectious etiologies such as herpes and mycoplasma infection.⁴⁴ Of cases due to drugs 16% to 26% are attributed to TMP/SMX.^{38,43}

An actual incidence of these diseases is difficult to ascertain because of their rarity. One of the largest population based studies of these 3 entities in the United States identified no cases of erythema multiforme due to TMP/SMX in a 15-year period.⁴⁵ Erythema multiforme in children secondary to TMP/SMX ingestion was reported in only 1 of 42 pediatric cases in a 20-year review from Switzerland.⁴⁶ Another retrospective review of 22 pediatric cases of erythema multiforme in France in a 25-year period identified no cases secondary to TMP/SMX.⁴⁷ Fortunately the disease process is self-limited and there have been no reported fatalities secondary to erythema multiforme in children.^{38,43} Treatment includes discontinuing the offending drug, antihistamines for symptomatic care, oral antacids for mucosal irritation and possibly systemic steroids.⁴⁴

SJS was first described in 1922 in 2 pediatric patients and it is now characterized by erythematous lesions with coalescence of lesions, detachment of the epidermis, mucosal involvement and less than 10% total body surface area involvement.^{42,48} The overall incidence of SJS in several large population studies was 1.2 to 6.1 per million person-years.^{45,49} Only 3 pediatric cases were reported, possibly implicating TMP or SMX in those studies.⁴⁹ A large study of 2,622 children on TMP/SMX showed 1 with SJS.³⁷ Treatment for SJS includes eliminating the offending agent, supportive care and possible transfer to a specialized burn center for the management of skin lesions. Mortality from SJS in pediatric patients has been reported to be 3.6%.⁴³

TEN was first described by Lyell in 1956 and it represents the rarest and most severe form of acute bullous disease.⁵⁰ Patients with TEN have skin lesions affecting greater than 30% of the body surface area and extensive epidermal detachment. The overall incidence of TEN has been reported at 0.4 to 1 cases per million person-years.^{45,51} Several small series of pediatric patients with TEN have been reported.^{52,53} Most children with TEN require referral to a specialized burn center. Mortality associated with TEN in children has been reported from 7% to 37%.⁵²⁻⁵⁵

Hematological toxicity. Hematological adverse reactions in children have been reported with the use of TMP/SMX.⁵⁶⁻⁵⁸ Despite the overwhelming selective binding of TMP and SMX to bacterial enzymes in vitro the 2 drugs were individually shown to cause a dose dependent decrease in erythroid and granulocyte-monocyte colony formation.⁵⁹ Uhari et al reported 0.7 and 0.2 blood dyscrasia events per 100 years at risk in 2 to 15-year-old children on long-term prophylaxis with TMP and SMX monotherapy, respectively.⁵ One study in children showed as high as a 72% rate of hematological side effects with neutropenia being the most common.⁵⁶ However, TMP/SMX was given parenterally (20 to 40 mg/kg daily) compared to the prophylactic dose (2 mg/kg daily).

The largest population study of 2,622 children on TMP/SMX showed no incidence of blood dyscrasias.³⁷ However, only 17% of the patients received more than 2 refills of the medicine and the actual dose was not reported. A prospective study of hematological adverse reactions in children after an oral 10-day course of TMP/SMX at a dose of 8 mg/kg daily showed that 34% had neutropenia and 12% had thrombocytopenia.⁵⁷ Smellie et al reported no hematological abnormalities in 106 children followed 2 to 10 years for recurrent UTI on prophylactic doses of TMP/SMX.⁶⁰

A purported role of underlying vitamin B12 or folic acid deficiency has been suggested by some groups.⁶¹ This mech-

anism deserves significant consideration since many children with an absent terminal ileum secondary to reconstructive surgery receive TMP/SMX for the prophylaxis or treatment of urinary infection. Fortunately to our knowledge there have not been any fatalities in children related to hematological adverse reactions. Discontinuation of the drug, and supplementation with folic acid and vitamin B12 have been associated with complete improvement in all cases. A role for routine hematological evaluation of patients on TMP/SMX is not supported by the literature unless there is an underlying risk of folate or vitamin B12 deficiency.

Hepatotoxicity. Sulfonamides and trimethoprim have been implicated together and separately in causing hepatic toxicity. Hepatocellular (40%), mixed (40%) and cholestatic (20%) injuries are the most commonly reported pathological subtypes in adults.⁶² The incidence of this adverse reaction has been reported to be 1/11,000 to 1/45,000 treatments.^{63,64} Contrary to findings in adults, there were no reports in children from the adverse drug reaction advisory committee in Sweden, where it is mandatory to report all adverse reactions to medications.⁶² Similar reviews from Finland and the United States showed no cases of hepatotoxicity in children.^{5,37} We identified 6 reports of hepatotoxicity involving children 16 months to 16 years old.⁶⁵⁻⁷⁰

Hepatotoxicity related to TMP/SMX has been suggested to be a hypersensitivity reaction. This is supported by the manifestation of a preceding rash or eosinophilia in all of these pediatric cases. Additionally, cutaneous hypersensitivity reactions, such as toxic epidermal necrolysis, are frequently associated with elevated liver enzymes in children.^{53,71} Perhaps the incidence of liver hypersensitivity reactions is greater than we suspect because many rashes resolve spontaneously after discontinuation of the drug and liver function tests are not routinely obtained.

Four pediatric patients whom we identified in the literature had resolution of hepatotoxicity with discontinuation of the drug, administration of steroids and supportive care.^{65,68,69} One patient progressed to liver failure and underwent orthotopic liver transplantation.⁶⁶ Another patient progressed to liver failure and died.⁶⁷ Of note, 1 of these patients was receiving the drug for UTI prophylaxis and survived. One patient was on TMP monotherapy and also survived.^{65,68}

Somatic growth. The effect of TMP/SMX on somatic growth has been raised based on some experimental evidence in animals. Smellie et al evaluated 114 girls 2 to 12 years old receiving long-term (6 months to 6 years), low dose (2 mg/kg TMP daily) prophylactic TMP/SMX.^{60,72} They found no difference in somatic growth, growth velocity or weight compared to age matched controls. Similar findings were noted in a study of children who underwent 1 year of antibacterial prophylaxis and subsequent surgery for vesicoureteral reflux.⁷³

HIV. The incidence of adverse reactions to TMP/SMX in patients with AIDS is reported to be around 40%.^{74,75} Patients with HIV rely on sulfonamide therapy for *Pneumocystis carinii* pneumonia prophylaxis at higher doses (5 mg/kg daily) than urinary prophylaxis (2 mg/kg daily). Since the incidence of adverse drug reactions is so high in children who are HIV positive, some groups have advocated HIV testing all children who present with adverse reactions to TMP/SMX.

DISCUSSION

Medical management of reflux, hydronephrosis and dysfunctional voiding has allowed many children to avoid surgery. Long-term, low dose antibiotics have become the primary component of medical management. In addition to a better understanding of the disease process, the success and safety of these drugs has led to the decreased application of urethral dilation for dysfunctional voiding and ureteral re-

implantation for reflux. The use of antibiotics has also affected treatment in infants and children with megaureters, ureteroceles and hydronephrosis. Antibiotics have allowed us to observe safely many diseases and with time determine who requires surgery.

Despite the reported side effect profile in adults, NFN, TMP and SMX are safe in the pediatric population. As seen from the evidence presented in this review, severe adverse reactions, such as pulmonary fibrosis associated with NFN and SJS/TEN associated with TMP/SMX, occur rarely in children. Adverse reactions are seen much more commonly in older patients with comorbidities and polypharmacy. Other reactions, such as hematological toxicity associated with TMP and SMX, are rarely seen in children on low prophylactic doses. The more common side effects, such as rashes associated with TMP and SMX, and gastrointestinal upset associated with NFN, are mild and self-limiting with discontinuation of the medicine. Although the side effect profile of TMP alone appears better than that of the TMP/SMX combination, the increased risk of breakthrough infection in children with reflux or scarring should be considered.

The long-term use of low dose antibiotics for urinary prophylaxis is safe. Unfortunately the media has impressed on the public that antibiotics are not always appropriate and can be unsafe for society as a whole. With increasing microbial antibiotic resistance the overuse of antibiotics has certainly been detrimental to the population. Most patients have not analyzed this information and have not discriminated between treating otitis, the common cold and UTI. When presented with the recommendation of long-term antibiotic use, they frequently assume that this is unsafe for the child.

A misunderstanding of this information as well as recent advances in minimally invasive surgery has led some groups to believe that early surgery may be safer than long-term antibiotics. In particular, the subureteral polytetrafluoroethylene injection procedure has been advocated and promoted as an alternative to medical management of low grade reflux. We strongly disagree with this recent trend. There is no better repair of vesicoureteral reflux than that which occurs in most children on medical management. The natural maturation of the ureterovesical junction that occurs with spontaneous resolution is enduring and safe. There is no data to suggest that general anesthesia, a preoperative high dose parenteral antibiotic and surgery are safer than long-term, low dose urinary prophylaxis.

The indications for and alternatives to antibiotic therapy should be explained to parents. If necessary, the effect of antibiotic use on a population vs an individual should be discussed. For their child successful urinary prophylaxis will obviate the treatment of infections with high dose antibiotics. Parents should be informed and educated about the potential for side effects. The extremely low incidence and reversibility of significant adverse reactions should be stressed. A better understanding and awareness of the potential adverse reactions will improve outcomes and increase overall safety for children.

CONCLUSIONS

The use of prophylactic NFN, TMP and SMX is safe in children for long-term therapy. The antibiotic safety issue should not be misconstrued as an argument for surgical therapy, whether minimally invasive or not. Adverse reactions exist to these medicines but they are less common than seen in adults, presumably because of the lower dose used for prophylactic therapy, and the lack of significant comorbidities and drug interactions in children. Serious side effects are extremely rare and most are reversible with discontinuation of therapy. The extremely low potential for significant adverse reactions should be discussed with parents.

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